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Research Paper

Assessing Electrocardiographic Parameters in the Patients With Drug-resistant Temporal Lobe Epilepsy: A Case-control Study

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ABSTRACT

Introduction: Sudden, unexpected death in epilepsy (SUDEP) is a substantial cause of death in patients with epilepsy. Although electroconductive disorders leading to life-threatening arrhythmia are supposed to play a crucial role, there is a paucity of knowledge in variables among the patients with drug-resistant temporal lobe epilepsy (TLE) compared to the healthy controls.

Methods: The current case-control study has been conducted on 50 drug-resistant TLE patients as the cases and 50 age- and gender-matched healthy subjects selected from their first-degree family members. Electrocardiographic (ECG) were taken from the cases when admitted at the hospital (baseline), immediately after a seizure incidence, and within an hour after the end of the seizure and compared with a random ECG of the controls considering parameters, including PR-, RR-, and corrected QT interval (QTc), P wave duration, and heart rate (HR) variability.

Results: A shorter corrected QTc interval was notified among the drug-resistant TLE patients compared to the controls (P=0.017) in the baseline taken ECGs, while the assessments immediately after the seizure revealed significant differences in terms of RR-interval (P=0.005) and HR (P=0.005). Postictal ECGs did not differ between the groups (P>0.05).

Conclusion: According to the findings of this study, shortened QTc interval at baseline ECGs, shortened RR interval, and increased HR during the seizure were the ECG elements that affected drug-resistant TLE patients; however, to generalize the outcomes, further studies are required.

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Highlights

- The drug-resistant TLE patients had a shorter QT interval than controls at the time of admission to the hospital.
- The drug-resistant TLE patients had a shorter RR interval and increased heart rate than controls immediately after seizure.
- One hour after seizure, there were no significant differences in ECG findings between the groups.

Plain Language Summary

Sudden unexpected death is common in patients with temporal lobe epilepsy (TLE), especially in drug-resistant patients. This study aimed to evaluate the ECG changes in patients with drug-resistant TLE compared to healthy people. Their electrocardiographic (ECG) parameters, including PR-interval, RR-interval, corrected QT interval, P wave duration, and heart rate, were measured at the time of admission to the hospital (baseline), immediately after seizure, and one hour after the seizure. The results showed that, at baseline, only the difference in QT interval was significant between the two groups. Immediately after seizure, the difference in RR interval and heart rate was significant. There were no significant differences between the groups one hour after seizure. The drug-resistant TLE patients had a shorter QT interval at baseline and a shorter RR interval and increased heart rate immediately after seizure compared to healthy people.

1. Introduction

Sudden, unexpected death in epilepsy (SUDEP) is a substantial cause of death in patients with epilepsy (PWE). SUDEP is defined as non-accidental, non-suicidal death in the absence of documented status epilepticus or any other identifiable causes (Nashef et al., 2012). This condition can occur at any age but primarily affects younger adults. The annual incidence rate of SUDEP differs according to the studied population, but it ranges from 0.35 to 9.3 per 1000 persons (de Sousa et al., 2017; Kolsal et al., 2014). The risk of SUDEP increases considerably among drug-resistant PWE (Vilella et al., 2019).

Epileptic seizures are accompanied by autonomic function alterations that can affect respiratory, cardiovascular, gastrointestinal, urinary, and genital systems during the phase of epilepsy or early in the ictal phase (Liedholm & Gudjonsson, 1992; Nousiainen et al., 1989). The cardiovascular system is the most noted system of the body due to its most crucial potential role in SUDEP. However, recent studies have focused on respiratory depression following seizures as a common cause of improper oxygenation (Asadollahi et al., 2019).

For a long time, scientists have been searching for an ambulatory, non-invasive, applicable means to detect or forecast seizure incidence (Bruno et al., 2018). Electrocardiographic (ECG) studies have achieved valuable outcomes. Significant increases in heart rate (HR) immediately before seizure initiation have been noted in 64%-100% of the patients and ignited a theory regarding vagal stimulation to prevent or shorten the seizure duration (Boon et al., 2015; Leutmezer et al., 2003).

Cardiac arrhythmia is another factor that may contribute to SUDEP. Studies in the literature have represented that patients with recurrent seizures are at two to threefold increased risk of arrhythmia development. A prospective long-term study showed that one-fourth of the PWE had clinically significant cardiac arrhythmia, even if no cardiac risk factor was detected (Lamberts et al., 2015; Surges et al., 2010).

The underlying reason for cardiac variabilities in preseizure, seizure, and postictal phases is primarily attributed to catecholamine release and then to the stimulated site of the brain (Mativo et al., 2010; Myers et al., 2018).

Cortical-stimulation studies notified that the left insular cortex was responsible for cardiovascular depressor response and bradycardia. Surprisingly, the opposite side acted as a stimulatory part. This characteristic was reinforced when ictal tachycardia was found by the occurrence of right hemispheric seizures in temporal lobe epilepsy (TLE) patients. However, further confirmatory investigations are required. The other part of the brain supposed to play a key role in neural regulation of the

HR and rhythm is the amygdala; however, further human studies revealed that the amygdala's role in affecting cardiac function was not to the expected extent. Nevertheless, widespread involvement of the unilateral limbic system is required to (Leutmezer et al., 2003) modulate cardiac function remarkably.

Most previous studies have focused on ECG alternations in the preictal period. We conducted this study to evaluate the ECG changes in patients with drug-resistant TLE immediately by the end of the seizure and then within an hour after the postictal phase.

2. Materials and Methods

This case-control study was conducted on 50 drug-resistant TLE patients admitted at Kashani Hospital, a referral center of neurologic disorders affiliated with Isfahan University of Medical Sciences, Isfahan City, Iran, from January 2018 to December 2019.

The case group with documented drug-resistant TLE by an expert epileptologist was included. The diagnosis was made using magnetic resonance imaging (MRI), video electroencephalography (EEG) monitoring, and medical history.

The controls were selected from the age- and gender-matched first-degree family members of the patients who lacked a history of seizure or epilepsy. Less than 18 years of age, flawed medical records, and any history of cardiovascular diseases, hypertension, diabetes mellitus, dyslipidemia, and cardiac anomalies were determined as the exclusion criteria.

The studied patients were recruited by convenience sampling, and the control group that met the study criteria was selected until the desired number of the studied population was achieved.

The demographic information of the study population, including age, gender, epilepsy age of onset, and marital status, was recorded in the study checklist. Furthermore, the epileptic characteristics, including the duration of the seizure, age of onset, seizure frequency (daily, weekly, monthly, annually, or others), seizure semiology (dialeptic, automotor, focal and secondary generalized), positive family history, involved part of the brain based on MRI (hippocampal sclerosis, temporal atrophy, temporal gliosis, temporal glioma, temporal heterotopia) and medications (sodium valproate, carbamazepine, levetiracetam, phenytoin, phenobarbital, lamotrigine, and topiramate) were entered into the checklist.

Standard 12-lead electrocardiography (ECG) was taken from the cases at baseline (when admitted to the hospital) immediately by the end of the seizure and within an hour after the postictal phase. Similarly, standard electrocardiography was taken from the controls.

A cardiologist interpreted the ECGs. The normal ranges of the assessed parameters were determined as RR interval of 0.6-1.2 s, PR interval of 0.12-0.2 s, QTc of 0.35 to 0.44 s for men and from 0.36 to 0.46 s for women that is calculated from Bazett formula (Equation 1):

1. $QTc = QT / \sqrt{RR}$,

ST segment depression and elevation for more than 0.2 mV from the isoelectric line and P wave duration of less than 0.12 s and 1-1.4 mV height.

The ECGs were assessed regarding arrhythmia, including atrial fibrillation, sinus tachycardia or bradycardia, premature atrial depolarization, premature ventricular depolarization, branch blocks, and supraventricular arrhythmias.

The obtained data were entered into the SPSS software, version 15 (SPSS Inc., Chicago, IL, USA). The descriptive data were presented in mean, standard deviation, absolute numbers, and percentages. A chi-square test was utilized to compare the frequencies between groups. The continuous variables were compared using a t-test. A P value of <0.05 was defined as the level of significance.

3. Results

The current study has been conducted on 50 drug-resistant temporal lobe epileptic patients and 50 other normal patients as the control group. The case group predominantly consisted of males (52%); half of them (50%) were married and had a mean age of 32.88±1.91 years (range: 18-73 years old). The comparison of demographic characteristics of the cases and controls is demonstrated in Table 1. Given that, the two groups were similar regarding their age (P=0.058) and gender distribution (P=0.84), but their marital status was different (P<0.001).

Table 2 represents the epilepsy-related characteristics in the case group.

Table 1. Demographic characteristics of the studied groups

Variables		Mean±SD/No. (%)		P
		Case Group (n=50)	Control Group (n=50)	
Age (y)		32.88±1.91	36.66±7.19	0.058*
Gender	Female	24(48)	25(50)	0.84**
	Male	26(52)	25(50)	
Marital status	Single	25(50)	5(10)	<0.001**
	Married	25(50)	45(90)	

*T-test, **Chi-square test.

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Table 2. Epilepsy-related characteristics

Variables		Mean±SD/No. (%)
Age of onset		14.35±13.76
Epilepsy duration		18.57±11.67
Positive family history of epilepsy		12(24)
Epilepsy semiology	Dialeptic	16(32)
	Automotor	29(58)
	Focal	27(54)
	Secondary generalized	8(16)
Medications	Sodium valproate	32(64)
	Carbamazepine	29(58)
	Levetiracetam	34(68)
	Phenytoin	3(6)
	Phenobarbital	10(20)
	Lamotrigine	5(10)
	Topiramate	10(20)
Type of lesion in MRI	Mesial temporal sclerosis	25(50)
	Temporal atrophy	1(2)
	Encephalomalacia	1(2)
	Temporal tumor	4(8)
	Temporal gliosis	1(2)
	Temporal heterotopia	1(2)

Variables		Mean±SD/No. (%)
Seizure frequency	Daily	6(12)
	Weekly	12(24)
	Monthly	20(40)
	Annually	2(4)
	Variable	8(15)

MRI: Magnetic resonance imaging.

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Based on the ECG assessments of the patients, a shorter corrected QTc interval was noted among drug-resistant TLE patients compared to the controls (P=0.017) in baseline assessments. Immediately after the seizure, the evaluations revealed significant differences in RR interval (P=0.005) and HR (P=0.005). The ECG assessment within an hour after the end of the seizure did not differ between the groups.

ST-segment alterations, including elevation or depression, were noted in 3 cases (6%) (1 depression and 2 elevations) immediately after the seizure and 2 cases (4%) after an hour. None of the controls represented ST-segment changes in any assessment. The comparison of the groups revealed insignificant differences immediately after the seizure (P=0.24) and within an hour (P=0.49). All the ST-segment alterations were early depolarization but not ischemic changes (Table 3).

Furthermore, the assessment of electrocardiograms to find arrhythmia revealed nothing compatible with arrhythmogenic manifestations in any of the cases or controls.

The patient's age was not associated with any ECG abnormalities changes (Table 4).

Table 3. Comparing ECG findings between the studied groups

Group	Baseline			Immediately After the Seizure			Within an Hour After the Seizure		
	Case	Control	P*	Case	Control	P*	Case	Control	P*
PR interval	120 (120, 160)	120 (120, 160)	0.225	120 (120, 160)	120 (120, 160)	0.496	120 (120, 160)	120 (120, 160)	0.678
RR interval	780 (710, 840)	800 (735.5, 852)	0.524	700 (600, 840)	800 (735, 852.5)	0.005	760 (640, 850)	800 (735, 852.5)	0.074
QTc interval	320 (320, 360)	360 (320, 360)	0.017	360 (320, 360)	360 (320, 360)	0.125	360 (320, 360)	360 (320, 360)	0.278
HR	76.50 (71, 84.25)	75 (70, 81.5)	0.558	85.50 (71, 100)	75 (70, 81.5)	0.005	79 (70.75, 93)	75 (70, 81.5)	0.083
P wave duration	80 (80, 80)	80 (80, 80)	0.708	80 (80, 80)	80 (80, 80)	0.258	80 (80, 80)	80 (80, 80)	0.755

*The Mann-Whitney U test.

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Table 4. Assessing age role in ECG abnormality

Variable		Immediately After the Seizure			Within an Hour After the Seizure		
		Mean±SD		P	Mean±SD		P
		Normal	Abnormal		Normal	Abnormal	
Age	RR interval	34.09±12.85	30.53±9.77	0.322	33.66±11.96	29.33±11.70	0.329
	QTc interval	32.63±11.90	45±0.0	0.309			
	ST segment	32.87±12.08	33±10.81	0.896	32.63±12.08	39±4.24	0.464

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4. Discussion

Our investigation revealed that the cases, the patients with drug-resistant TLE, and the controls, their first-degree healthy family members, significantly differed regarding their QTc interval when they had no seizure. In contrast, the cases' HR was remarkably higher by the end of the seizures, and the RR-interval was significantly lower than the controls. Nevertheless, the ECGs taken within an hour after the seizure revealed insignificant differences.

SUDEP seems to occur due to an electrical event following a fatal cardiac arrhythmia; nevertheless, the exact etiology of SUDEP remains unknown and may be multifactorial (Cheung & Hachinski, 2000). The lethal cardiac arrhythmia may be initiated ictally or just in the interictal period (Teh et al., 2007). Another hypothesis regarding the mechanism by which SUDEP occurs refers to prolonged hypoxemia or hypercapnia in the ictal phase that leads to persistent acidosis, bradycardia, and, eventually, asystole (Goldman, 2015). Various contributing factors that interfere with the myocardium's normal de- or repolarization activity may be attributed to this sudden death in PWE (Asadollahi et al., 2019).

P wave and PR interval were in the normal range in both cases and controls of our study, which is consistent with the study by Asadollahi et al. (2019); however, an insignificant increase in PR interval was found in their investigation among the PWE both interictally and in the postictal phase. Other previous studies have noted The elongated PR interval, particularly among those with generalized epilepsy (Nei et al., 2012). One of the strong theories about the localization of arrhythmia in PWE targets atrioventricular conduction block due to disrupted depolarization (van der Lende et al., 2016).

The QT interval is one of the popular elements of ECG accused of the incidence of arrhythmia in PWE. Shortness of QT interval occurs because of disrupted cardiac repolarization. QTc interval was remarkably lower in PWE cases than the controls in ECGs taken at the baseline. This finding is consistent with most of the studies in the literature representing shortened QT interval (Ramadan et al., 2014; Surges et al., 2010), while some investigations presented no or mild alterations in QT interval (Drake et al., 1993; Lamberts et al., 2015). These controversial outcomes are age, study population, risk factors, and epilepsy types.

The shortness of the QT interval reflects the acceleration of repolarization, which is an outcome of either increased or decreased depolarizing currents (Tse et al., 2017). The irregular shortness of the QT interval is accompanied by a reduced ventricular muscle refractory period and an increased risk of reentrant tachycardia development (Surges et al., 2010). Ion channelopathies, alteration in His-Purkinje network distribution, and changes in intracellular communication are the probable mechanisms by which a shortened QT interval can lead to a life-threatening arrhythmia (Brotherstone et al., 2010; Tse et al., 2017).

A shortened RR interval during the seizure was notified between the case and control groups. De Sousa et al. presented an insignificant difference in their case-control study (de Sousa et al., 2017). In contrast, the latter study by Asadollahi et al., in line with ours, presented a significantly shorter RR interval in PWE than the control group. This finding was noted in all types of epilepsies, including generalized TLE and frontal lobe epilepsy (Asadollahi et al., 2019).

Catecholamine release by seizure affects HR variability, which is associated with RR interval variabilities. The significance of the RR interval is due to its role in HR variability, which is affected by a shortened RR interval. On the other hand, a shortened RR interval is representative of autonomic nervous system function (Myers et al., 2018; Thuraisingham, 2006). Therefore, a significant deviation in the RR interval shows autonomic dysfunction during the seizure presented in both focal and generalized seizures (Mativo et al., 2010; Ronkainen et al., 2006). The shortened RR interval immediately by the end of the seizure reflects tachycardia during and in the early ictal phase, confirmed in numerous studies representing increased HR in up to 100% of the PWE (Mayer et al., 2004; Ufongene et al., 2020).

We observed that the age of the patients was not associated with ECG abnormalities; however, Leutmezer presented an increased risk of life-threatening ECG abnormalities in younger adults (Leutmezer et al., 2003).

5. Conclusion

According to the findings of this study, shortened QTc interval at the baseline ECG, shortened RR interval, and increased HR during the seizure were the ECG elements affected in drug-resistant TLE patients; however, to generalize the outcomes, further studies are required.

Study limitations

The small number of the studied population and the observational design of our study are the most remarkable

limitations of this study. Further studies that consider the probable confounders are strongly recommended.

Ethical Considerations

Compliance with ethical guidelines

The study proposal that met the Helsinki Declaration criteria was approved by the Ethics Committee of Isfahan University of Medical Sciences. The study protocol was explained to the patients, their legal guardians, and the control group. They were reassured about the confidentiality and signed written consent for participation in the study.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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